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Abstract

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PI Name: KATZENELLENBOGEN, JOHN A.

PI Email: JKATZENE@UIUC.EDU

Project Title: Screen for Coactivator Binding Inhibitors to Block Estrogen Action

Abstract: *DESCRIPTION (provided by applicant):* The overall aim of this research is to identify novel compounds that can act as effective coactivator binding inhibitors (CBIs) to block gene activation through the estrogen receptors, ERa and ERa, by directly inhibiting their interaction with important coregulator proteins. The ERs well validated targets for women's health and breast cancer prevention and treatment. The CBIs are not targeted at the traditional site on the ERs, namely, the ligand binding pocket; rather, their target is a hydrophobic groove through which the ERs interact with the coactivator proteins of the p160 family, the steroid receptor coactivators SRC1 and SRC3, critical mediators of estrogen signaling and the regulation of gene transcription by the ERs. By blocking estrogen signaling through ERa and ERa by direct competition with their binding to SRC1 and SRC3 in the hydrophobic groove rather than indirectly by competitive ligand-based antagonism within the ligand binding pocket, we hypothesize that we will be able to achieve a more complete blockade of estrogen action and possibly overcome the development of resistance to endocrine therapy that typically occurs in the treatment of breast cancer both with antiestrogens and aromatase inhibitors. In the past, we have used structure-based design to guide the preparation of CBIs, and we have developed fluorescence-based assays to measure CBI activity. While we have found CBIs with Ki values in the 5-20 fM range, we have not succeeded in finding CBIs having nanomolar potencies. We now propose to work with members of the Molecular Libraries Screening Centers Network (MLSCN) to refine a time-resolved fluorescence resonance energy transfer (TR-FRET) assay and use it to screen large compound libraries in a much broader search for hits of novel structure. After confirming these hits in mechanistically appropriate counter screens and alternative assays of CBI activity and selectivity, we would plan to optimize them by medicinal chemistry approaches, to obtain receptor-specific CBIs that have nanomolar affinities, so that in future studies they can be used in cell-based and animal assay systems at concentrations and doses that will not be toxic. This cooperative assay development/molecular library screening work will also provide a basis for expanding the search for CBIs that are specific for other nuclear hormone receptors or those that block ER interaction with other proteins that might be mediating the development of endocrine resistance in breast cancer therapy.

Thesaurus Terms: coactivator binding inhibitors, CBI, estrogen receptor, Era, coregulator proteins, breast cancer, p160, SRC1, SRC3, estrogen signaling, antiestrogens, aromatase inhibitors, fluorescence-based assays, Ki, Molecular Libraries Screening Centers Network, MLSCN, time-resolved fluorescence resonance energy transfer, TR-FRET

Institution: UNIVERSITY OF ILLINOIS
600 S. MATHEWS AVE., BOX 37-5
461 ROGER ADAMS LAB
URBANA, IL 618013792

Department DEPARTMENT OF CHEMISTRY

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